

September 13, 1946.

Dear Dr. Edwards:

First let me thank you for a very constructive reply to what was perhaps a prejudicially one-sided presentation of the case that I had sent in my last letter. I do, however, disagree with your concluding paragraph, that we are talking at cross-purposes and do not understand each other. Bacteria are only since very recently under genetic study, and it is not at all unlikely that new concepts of inheritance will have to be erected. We must, however, start on the basis of what is already known, and interpret new findings in the light of this when they appear, rather than abandon existing concepts in favor of a vague formulation of the capacity of bacteria to be coaxed. Spiegelman (at Washington University) is doing a classical piece of research on adaptive enzymes, primarily in yeasts, which is tying together the older genetic ideas with these most interesting phenomena.

I am particularly interested in your observation that induced variation by a serum may not necessarily be exactly associated with its agglutinin content. It would be of the very greatest importance to elucidate the mechanisms of this process, both from an academic genetical, and a practical point of view.

Phage adaptations have, I think, been shown fairly clearly to be instances of random variation (Luria, Genetics, 1945.)

Please do not get the impression that I have a cause that I am trying to impress on you, sir. With your cordial cooperation (as so far evidenced) I am trying to apply certain processes and principles that were developed with nutritional mutants in *E. coli*, to the inheritance of antigenic characters in *Salmonella*. To that part of it, I doubt that a priori argument is any

longer fruitful.

So far, I have had the opportunity to study about 120 strains from the Hartford Laboratories for their nutritional requirements. Most *Salmonella* strains are apparently prototrophic, i.e. have very simple requirements, growing well on a basal synthetic medium. *Salmonella pullorum* strains evidently require leucine and cystine fairly consistently, with some variations, and some other *Salmonellas* seem to require only a source of reduced sulfur. There may, however, be a few naturally occurring strains with well marked requirements that can be used as discussed previously. One of these is a paratyphi strains which requires tryptophane and methionine. Attempts to get prototrophs by crossing this with *pullorum* have not, however, been successful.

I am enclosing a reprint of some of our *Neurospora* work which may be of interest as the basis of some the ideas which I expressed about 'induced variation.' It would be very desirable to visit you at Lexington, and I shall if that seems possible.

Very sincerely yours,

Joshua Lederberg.